REMARKS

Reconsideration and withdrawal of the rejections of the claims are requested in view of the following remarks, which place the claims in condition for allowance.

The Examiner is thanked for indicating that the objection to the specification and claims, the rejection under 35 U.S.C. § 112, second paragraph in part, and the rejection on the ground of nonstatutory obviousness-type double patenting in part have been withdrawn.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100 and 101 are under consideration in this application. Claim 101 is amended to clarify the structure of Formula I. Support for the amendment to claim 101 can be found on page 6, lines 23-25, and in view of the amendment to the specification filed on May 29, 2007 and entered by the Examiner.

No new matter is added.

It is submitted that the claims herewith are patentably distinct over the prior art, and these claims are in full compliance with the requirements of 35 U.S.C. § 112. The amendments to the claims presented herein are not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply to clarify the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that these amendments should not give rise to any estoppel, as they are not narrowing amendments.

II. THE REJECTIONS UNDER 35 U.S.C. § 112 ARE OVERCOME

Enablement

Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, and 100 were rejected under the first paragraph of Section 112 as allegedly lacking enablement. The rejection is traversed.

The Examiner alleges that the recitation of inhibitors of presenilin or presenilin-dependent gamma secretase encompass almost any agent and almost any means, and that there is no structural and little functional language recited in the claims. The Examiner also contends that there is no teaching of the common structure/characteristics that are required for the agent that down-regulates the Notch signaling.

In response, it is respectfully argued that the present invention is indeed enabled and that one of ordinary skill in the art can perform the method of the present invention without undue experimentation. The specification, notably on pages 33-35, sufficiently describes inhibitors that can be used in the present invention. The specification also provides guidance as to the assays that can be performed to identify presenilin or presenilin-dependent gamma-secretase inhibitors (page 50-66), and working examples which demonstrate how the inhibitors can be used in the claimed method. Hence, the skilled artisan can perform the claimed invention by using the assays in the specification to identify the gamma-secretase inhibitors and the Examples to confirm that the inhibitors can be used to decrease regulatory CD4+ T cell activity.

Also, at the time of filing, various types of gamma-secretase inhibitors were known in the art, as exhibited in Doefler and Strooper. While the Examiner alleges that there is no teaching of a common structure/characteristic among the inhibitors, one skilled in the art would recognize that gamma-secretase inhibitors can differ in structure but still have inhibitory function (see Doefler, page 9315, right column, third complete paragraph). This reflects the nature of the art, wherein the structure and potency of the active agent have less importance and the functional activity is emphasized. This also suggests that the level of skill by one in the art would encompass performing assays to identify presenilin or presenilin-dependent gamma-secretase inhibitors.

With all of this in mind, one skilled in the art would not be subjected to undue experimentation to practice the claimed invention in light of (i) the guidance in the specification, which sufficiently describes presenilin or presenilin-dependent gamma-secretase inhibitors and assays for identifying them; (ii) the working examples, which demonstrates how the inhibitors can be used in the claimed methods; and (iii) the state of the art at the time of filing, wherein examples of gamma-secretase inhibitors and the relationship, or lack thereof, between structure and function were known.

Written Description

Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, and 100 were rejected under the first paragraph of Section 112 as allegedly failing to comply with the written description requirement. The rejection is traversed.

The Examiner alleges that Applicants fail to demonstrate possession of the genus of inhibitors that can be used in the claim method. Also, the Examiner refers to claim 5 and contends that there is no demonstration of the genus of agents that can down-regulate the Notch signaling.

In response, it is asserted that the specification does indeed support the inhibitors that are disclosed in the claims. As mentioned above, the specification discloses inhibitors that can be used in the claimed method and assays that can be employed to identify such inhibitors. Moreover, according to the state of the art at the time of filing as exemplified by Doefler, it was known that active agents for inhibiting gamma-secretase can vary in structure, which emphasizes that the genus of inhibitors must be characterized by their function. With this in consideration, and given the nature of the field, there is ample demonstration that Applicants were in possession of the claimed invention at the time of filing.

The specification also provides adequate support for the "agent that down-regulates the Notch signaling pathway" as recited in claim 5. Notably, the specification provides examples of such agents on page 7, lines 16-20, and on page 45, line 26 – page 47, line 18. Therefore, these exemplified agents provide adequate support for the invention disclosed in claim 5.

Indefiniteness

Claim 101 stands rejected under the second paragraph of Section 112 as allegedly being indefinite. The rejection is traversed.

The Examiner alleges that the recitation of chemical formula "MW167 having Formula I" does not describe its precise structure. In response, claim 101 is amended to recite the structure identified as Formula I.

Reconsideration and withdrawal of all of the rejections under Section 112 are requested.

III. THE DOUBLE-PATENTING REJECTIONS ARE PROVISIONAL

Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, and 100 were provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over a number of co-pending applications. Applicants request that these rejections be held in abeyance until conflicting claims are patented.

IV. THE REJECTION UNDER 35 U.S.C. § 102 IS OVERCOME

Claims 1, 3-5, 30, 33, 42, 47, 49-51, 53-57, 60, 61, and 100 were rejected under Section 102(b) as allegedly being anticipated by Doefler, *et al.* (PNAS 98: 9312-9317, 2001; hereinafter "Doefler"). The rejection is traversed.

According to the Examiner, Doefler relates to a method of decreasing CD4+ T cells activity by an inhibitor of presenilin-dependent gamma-secretase, and allegedly shows that the

inhibitor blocks T cell development by inactivation of Notch-1 in fetal thymic organ cultures. However, as conceded by the Examiner, Doefler does not teach that the inhibitor can induce a decrease of CD4+ regulatory T cells activity. The Examiner employs Hoyne, *et al.* (Immunol Rev 182: 215-227, 2001; hereinafter "Hoyne") to demonstrate that activation of the Notch signaling pathway has effects on regulatory T cells and thereby modulates maturation of CD4+ T cells. Notably, Hoyne only discusses the effects of Notch signaling on naïve T cells and their differentiation into regulatory T cells, and does not suggest the effects on regulatory T cell activity. Further, it is apparent that the T cells in Doefler did not comprise regulatory T cells, since the T cells of Doefler were extracted directly from thymic lobes of embryos and not from peripheral tissues where regulatory T cells reside.

Further, Doefler measured T cell development and not T cell activity. Doefler indicates that the objective of the study was to examine thymocyte development (page 9313, left column, first paragraph) and this was achieved by staining the thymocytes with antibodies of cell markers related to cell differentiation (page 9313, left column, third paragraph). Doefler does not teach or suggest any method of measuring regulatory T cell activity, e.g., expression of cytokine. Therefore, Doefler does not teach a method of decreasing regulatory CD4+ T cell activity as claimed in the present invention.

Accordingly, reconsideration and withdrawal of the Section 102 rejection are requested.

IV. THE REJECTION UNDER 35 U.S.C. § 103 IS OVERCOME

Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100, and 101 were rejected under Section 103(a) as allegedly being unpatentable over Doefler in view of Strooper, *et al.* (Nature 398: 518-522, 1999; hereinafter "Strooper") and Lamb, *et al.* (WO 01/35990; hereinafter "Lamb"). The rejection is traversed.

The Examiner contends that, in light of the cited references, it would have been obvious to downregulate the Notch signaling that is involved in tumorgenesis or infection by an inhibitor of presenilin-dependent gamma-secretase or a combination of the inhibitor with a tumor antigen in order to enhance a productive immunity against tumor of infection.

As described above, it is asserted that Doefler does not teach or suggest a method of decreasing regulatory CD4+ T cell activity. The Doefler study only examines T cells from the

thymic lobe, while regulatory T cells are found in peripheral tissues. Also, Doefler studied T cell development and did not observe T cell activity.

Meanwhile, Strooper relates to inhibitors of presenilin-1 that block the release of Notch intracellular domain. As admitted by the Examiner, Strooper does not teach decreasing CD4+ regulatory T cells. Lamb relates to a method of enhancing T cells' reactivity to tumor cell by reducing expression of Notch ligand proteins, as expression of the Notch ligands can lead to the generation of regulatory T cells. Clearly, neither Strooper nor Lamb remedies the deficiencies in Doefler relating to inhibitors acting upon regulatory CD4+ T cells and decreasing their activity. Hence, the combination of Doefler, Strooper, and Lamb do not teach or suggest a method for decreasing regulatory CD4+ T cell activity as claimed in the present invention.

Therefore, one skilled in the art would not consider the present invention unpatentable in light of Doefler, Strooper, and Lamb. Reconsideration and withdrawal of the Section 103 rejection are requested.

CONCLUSION

The application is in condition for allowance. Favorable reconsideration and allowance of the claims are requested. The Examiner is invited to contact the undersigned if any outstanding issues may be resolved by telephone.

Respectfully submitted,

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